disease (COPD), and cancers such as leukemias, lymphomas, carcinomas, and the like, e.g. colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic, lung, breast, and prostate metastases, etc., to counter the renal damage and failure associated with ischemic conditions and the administration of certain drugs and radio active diagnostic and therapeutic agents, as well as a joint therapy with the administration of adenosine and adenosine-like agents in the treatment of arrhythmias such as SVT and in cardiovascular function tests (stress tests). The present agent is administered alone or before, during and after other treatments, including radiation, chemotherapy, antibody therapy, phototherapy, other cancer treatments, and surgery, either preventatively, prophylactically or therapeutically. --.

REMARKS

THE INTERVIEW

Dr. Epps is hereby thanked for her generosity and patience in awarding a most cordial, helpful and extended interview held with the applicant's attorney on March 31, 2000. During the course of the interview, the rejections issued by the examiner were discussed, and the attorney proposed amendments to the claims. Agreement was reached on the proposal and the fact that the claimed invention is patentably distinguishable over the references cited. The examiner withdraw the rejection of claims 8-13 under USC 1.103(a) over Nyce in view of Jacobson, as resulting from an error during processing of the Action. The following remarks contain the substance of the arguments exchanged during the interview and an expansion thereof.

THE PENDING CLAIMS

Claims 1-107 were pending and have been deleted, and claims 108-218 substituted therefor. Accordingly, Claims 108-218 remain pending in this case. Consideration and allowance of the submitted claims is requested.

THE SEQUENCE LISTING

During the interview, the examiner provided the applicant's attorney with a document requiring the correction of the sequence listing previously submitted, which

had not been mailed with the Action. The applicant is submitting a corrected Sequence Listing in paper and computer readable form, and a new Declaration with the language required by the examiner.

THE WITHDRAWAL OF RESTRICTION

The examiner's withdrawal of the requirement for restriction in view of the applicant's arguments is acknowledged, with thanks.

THE OBJECTIONS TO SPECIFICATION AND CLAIMS

1- Objections to the Abstract of the Invention

The examiner required a shortened Abstract.

The applicant is providing an abstract in compliance with the rules.

2- Objections to the Claims

Claims 8, 25-28, 30 and 83 stand objected to, for a variety of reasons.

The claims have been amended as agreed to during the course of the interview, except for the following claims. Claim 9 has been objected to as not further limiting claim 8. This is incorrect because whereas claim 8 may contain as little as one analogue-substituted A, all As are substituted by an analogue in claim 9. This is a further limitation imposed by the latter claim. Claims 25-28 are objected to as not further limiting claim 1. This is also incorrect. The composition of claim 1 comprises an oligo and a surfactant that either counters low levels of lung surfactant or enhances the uptake of the oligo. The surfactant in the composition is not present as a carrier but as an ingredient of the composition. Therefore, the carrier added by claim 25 et seq. does further limit the composition of claim 1. It should be noted that the surfactant may be present in a mixture with the oligo(s) or operatively linked to it (them). Support for this embodiment may be found, for example, at page 45, first paragraph. The "combinations" of oligos are meant to encompass strings of two or more oligos according to the invention, which are operatively linked. The applicant has provided the components of the trademarked surfactants requested by the examiner. The utilization of "in bulk" is a term of art that an

artisan would identify as signifying unseparated into unit doses, which separation then occurs at the time of preparation for administration or other use. As discussed during the interview, the text of the main method claim has been amended to refer to an "aerosol" composition, which is neither described nor suggested in the art.

The applicant believes that the above objections have been overcome.

3- The Specification

The specification has been amended to introduce the chain of priority and the relationship to the parent cases. In addition, the specification has been amended to correct clerical error incurred at the time of filing. Finally the specification has also been amended to add targets and exemplary oligonucleotides that were disclosed in one of the parent applications, USSN 08/474,497 filed June 7, 1995, now U. S. Patent No. 5,994,315.

THE INDEFINITENESS REJECTION

Various claims have been rejected under 35 U.S.C. 1.112, second paragraph, allegedly because the language of those claims are indefinite. This rejection is partially traversed.

The rejected claims have been amended to more clearly describe the claimed subject matter, except for claims 55-56, and 95. The surfactant has been described by its function in claims 1 and 57 (newly submitted claims 108 and 183). Support for this language may be found throughout the specification, particularly at page 44, last paragraph. The same claims include combinations of the oligos, which is a reference to multiple copies of the same of different oligos (already included in the definition of the oligo earlier in the text) operatively linked together. The term "bulk", in claim 56 is a terms of art and, therefore, has been maintained (naw claim 162). The terms "single and multiple unit" in claim 55 (now claim 161) has been amended by addition of the term "dose". Claim 95 (now claim 115) has been amended to specify that "if the oligo contains A", then the condition applies. Claims 122-123 have been amended to incorporate all substitutions described in the specification. Support for this may be found at page 43. These are known and tested substituents, and methods for their preparation and their

function are well known in the art and, thus, need not be further described here.

The examiner objected to the terms "lamellar bodies"; however, these are terms of art that refer to lipoid structures that are not strictly spherical as liposomes generally are. Claim 130 has been amended to contain solely these terms. Claims 131, 171- 172 and 182 have been amended to reflect a range of about 0.05 to about 50 microns and 0.5-10 and 10-500 micron particle size, as described at page 48, last paragraph, and page 49, third full paragraph.

Claim 173 has been amended as an independent claim, and is directed to the use of any and all anti-sense oligos that alleviate hypersensitivity to, or reduce levels of, adenosine, bronchoconstriction, allergy(ies) and/or inflammation in the form of an aerosol. This language is supported throughout the specification, for example at page 6, third paragraph.

The applicant is also amending the specification and the claims to incorporate the names of ingredients of the tradenamed surfactants previously provided. in claim 23 (new claim 130-131), and they will be incorporated into the claim as soon as they become available to counsel.

The examiner is invited to withdraw the above rejection in view of the amendments and the explanation provided by the applicant.

THE FIRST ENABLEMENT REJECTION

Claims 1-107 stand rejected under 35 U.S.C. 1.112, first paragraph, allegedly because the specification does not enable a broad administration of oligos anti-sense to any target gene or RNA. This ground is partially traversed.

The new claims have been drafted as indicated to the examiner in the course of the interview, and are beleived to be free from the above ground of rejection. Claims 108-172 are directed to a specifically described set of targets (adenosine receptor associated DNA and mRNA) and activities or symptoms associated with the targets and, therefore, not subject to the above rejection. The specification is fully enabling of this invention, as it teaches how to make and use the inventive product. In the method claims (claim 173 et seq.), an aerosol composition of an anti-sense oligo targeted to DNA or mRNA encoding a protein associated with hyper-responsiveness to and/or increased

levels of adenosine, bronchoconstriction, allergies and/or inflammation is administered to the airways of a subject to alleviate these symptoms. The applicant has shown that the aerosol formulation of this invention, containing solid or liquid oligo particles, provides unexpected results for its intended use. This is clearly demonstrated by the substantially lower doses of anti-sense oligo required for an effective response when compared by the ones utilized by the prior art. Enclosed re several Declarations submitted by the inventor in the parent applications, which provide experimental data on the administration of anti-sense oligos directed to different targets. These clearly demonstrates the broad applicability of the claimed method.

Claim 87 is said not to be enabled because it relates to a prophylactic method. The experimental results show that when the oligo(s) of the invention is(are) administered to a subject, it(they) inhibit "prophyllactically" the effects of later administered adenosine.

The above rejection is thus believed moot.

THE SECOND ENABLEMENT REJECTION

Claims 8-13 stand rejected under 35 USC 1.112, first paragraph, allegedly because the specification does not provide enablement for all the adenosine substitutents listed.

The examiner relies on the Crooke reference for her arguments. However, Crooke himself indicates that his comments relate to a hypothetical effect as evidenced by his stating that those **"factors that may influence experimental interpretations"** (emphasis added), and not to the inability of utilizing substituents or analogues to the bases, etc. See, page1 of Crooke. However, it should be noted that because the definition of the substituents in claims 8-9 (present claims 115-116) has a functional requirement, any compound that does not fulfill the requirements remains outside the scope of the claims. Moreover, whether or not the analogue or universal base has agonistic or antagonistic activity at the adenosine receptors, as well as the degree of activity, is routinely determined by means of well established tests. Finally, a plurality of analogues listed in claims 117, 119-120 are known in the art as are their preparation and use in the present field. There thus is no need to further enable them here.

For example, the Ali et al. reference of record in the case discusses adenosine as a

potential mediator of allergic asthma. However, the use of adenosine antagonists for treating asthma was known prior to the Ali et al.'s publication. Theophylline, for example, a bronchodilator and adenosine receptor antagonist has been applied to the therapy of asthma for at least 70 years now. See, for example, Farmer et al., Brit. J. Pharmacol. 95(2): 371 (1988); Marquardt et al., J. Allergy & Clin. Immunol. 78 (3 Pt 1): 462 (1986), of record in the parent application. However, neither the prior art at large, nor Ali et al., Crooke, Bennett, Jacobson or the '962 patent disclose or suggest the applicant's anti-sense oligos, their administration in the form of an aerosol to a target tissue, or their effectiveness in amounts far below those previously utilized in the art.

Moreover, the analogues or universal bases are not incorporated to replace adenosine because of their inherent anti-bronchoconstricting, anti-allergic or anti-inflammatory activities, but to avoid freeing adenosine upon the break-down of the oligo. Although the effect of the anti-sense oligo may be to alleviate the listed symptoms, when it is biodegraded in the subject's body it releases adenosine and adenosine, which compound has agonistic activity at the adenosine receptors. This activity, as is known in the art, will produce undesirable side effects in a subject in need of the present treatment.

Finally, Crooke himself provides arguments to counter the examiner's selected comments lifted from his article. For example, Crooke unequivocally states that "peptide nucleic acid polymers act anti-sense and transcription inhibitors, and are quite stable to nucleases and peptidases". See, page 38, second paragraph. Also, Crooke states that numerous 3' modifications enhance stability (page 34, first paragraph), a large number of C2, C4, C5 and C6 modified pyrimidines and other nucleoside analogues have been synthesized, incorporated into bases and evaluated, and a review article is cited (page 32, first full paragraph), ibid for purines (page 33, section 2), and oligo conjugates (section 3 at pages 33-34), and the like. Whether it is the applicant or others that have synthesized and tested some of the analogues is irrelevant. That is what Crooke reports on in his review article. Further, the claimed invention does not require that each and every base in the oligo actually bind to the corresponding base on the target nucleic acid.

In addition to the above, the applicant is making of record along with this response literature indicating the routine use and wide knowledge in the art of the so called "Universal bases". An artisan would know how to commercially purchase,

synthesize, test and use these known bases.

Finally, under the U.S. Patent Law it is sufficient to make a showing involving some members of a group or genus whereas it is not required to show that all compounds are active, nor that they all act efficaciously. It suffices to enable them in their preparation and exemplary use.

The above rejection is thus believed to be moot.

THE FIRST ANTICIPATION REJECTION

Claims 1-7, 15-17, 23-28, 30, 34-37, 40, 53-54, 65-75, 80-81, 83, 88-90, 94 and 102-103 styand rejected under 35 USC 1.102(b), allegedly because they are anticipated by Nyce et al, Nature 1997, Nyce et al., WO 96 40162A1 or Nyce et al. WO 96 40266A1. This ground of rejection is traversed.

This application claims priority to the filing date of its parent and grandparent applications, dating back to June 7, 1995, and all references cited were published after this date. In addition, the claimed invention is different from the cited references, and neither reference by itself, nor their combination render it obvious.

None of the cited references employ a surfactant as an ingredient of the composition, as done here. The claimed invention utilizes a surfactant to either replenish surfactant in a subject's lung(s) or to enhance the up-take of an oligo by the subject's cells. Not one of the cited references discloses or suggests this feature.

In addition to the data provided in the exemplary disclosure of the patent application as filed, the enclosed Nyce Declarations provide additional anti-sense oligo sequences, which are targeted to different segments of different receptor encoding mRNAs. The anti-sense oligos were designed and prepared as taught in the present application. Four of them are phosphorothioate anti-sense oligonucleotides and the last is a phosphodiester version of Oligo I. Their effects on diseases or conditions associated with bronchoconstriction and/or inflammation were tested in an experimental animal widely recognized by the scientific community as a suitable model for these conditions. The results provided in the enclosed Declarations show clearly unexpected results brought about by the administration of the anti-sense oligos of the invention. Some oligos have a phosphodiester backbone, while others have a phosphorothioate backbone. Both

were shown to be highly effective in countering the targeted symptoms. The findings reported in the Nyce Declarations fully enable the scope of the invention encompassed by the present claims, and distinguish over the prior art.

The applicant believes to have provided extensive disclosure and experimental data, to enable the scope of the present claims. He has provided anti-sense oligo sequences of different lengths, directed to different segments of receptor mRNA molecules associated with bronchoconstriction and/or inflammation, encompassed by the claims. The applicant has demonstrated the feasibility and efficacy of the agent and the therapeutic method of the invention with 100% success in a plurality of animal species for which the oligos exhibit specificity. The examiner indicated that there is a lack of predictability in the field of anti-sense therapy. In a field short in efficacy and predictability, clearly the applicant's success takes on an even more significant meaning. The applicant has provided a multiple showing that demonstrates that his anti-sense therapy directly administered to the airways may be conducted in a routine, predictable and successful manner.

The Nyce Declarations, along with the original exemplary disclosure and the Nature (1997) Nyce publication cited by the examiner, moreover, have shown efficacy in different animal species of different oligos in amounts within the scope of the dose range disclosed. The applicant has provided strong evidence that when the claimed agent is administered in accordance with the claimed method, it enters the cells in therapeutic amounts in a dose-dependent manner. All the experimental data on the claimed agent show its effectiveness, even in the absence of uptake inducers. However, in one embodiment of this invention the nucleic acid is attached to a molecule which facilitates cell uptake. The utilization of transport enhancers was known in the art prior to this invention, and is not at the core of the applicant's invention.

The surfactant in the composition of the invention, as the text of claim 108 states, either replenishes surfactant in the subject's lung or enhances the uptake of the oligo, which effect is neither described nor suggested by the art cited. Accordingly, not only do the cited references not anticipate the claimed invention, but in addition, neither do they render it obvious. In view of the above, the examiner is invited to withdraw the above rejection.

THE SECOND ANTICIPATION REJECTION

Claims 1-7, 10,14-18, 23-28, 30, 34-37, 40, 53-54, 65-75, 80-81, 83, 88-90, 94 and 102-103 stand rejected under 35 USC 1.102(b), allegedly as being anticipated by US Patent No. 5,320,962 to Stiles ("the '962 patent"). This rejection is also traversed.

The claimed invention requires the composition to contain an anti-sense oligo **and** a surfactant as an ingredient, the latter in an amount effective to replenish surfactant in the subject's lungs or to enhance the uptake of the oligo. This is nowhere described or suggested by the '962 patent.

The '962 patent is different from the claimed invention, and fails to render it obvious. The disclosure of the '962 patent is restricted to the adenosine A_1 receptor. In fact, the prior patent does not even mention the adenosine A_3 receptor. More particularly, the **'962 patent relates solely to the human adenosine A_1 receptor**, not to the adenosine A_1 receptor from any other species.

Thus, **anti-sense oligos generally described by the '962 patent are specific to the human adenosine A_1 receptor mRNA, not any of the other adenosine receptor DNA or mRNA**. See, Section 8, or col.1 of the '962 patent. In addition, the anti-sense sequences must bind specifically to one of the following three DNA sequences:

> (1) parts of introns 1 and 4, all of intron 3, and all of exons 2 and 4 (SEQ. ID No.:1),
> (2) part of intron 5 and all of exon 6 (SEQ. ID No.:3), and
> (3) part of exon 5 or the cDNA (SEQ. ID No.:5).

See, col. 13, ls. 15-34, and col. 14, ls. 4-7 of the '962 patent. The claims, though, require the anti-sense oligos to specifically hybridize to **introns** 1 to 5 of the gene encoding the human adenosine A_1 receptor (SEQ. ID No.: 6) **under highly stringent conditions**. See, (b) of Claim 17 of the '962 patent. Although those conditions are utilized in vitro, they could never have been intended for in vivo administration: they are simply not encountered in the cell environment of a living subject. Thus, the '962 patent also fails to teach how to administer the oligos to a living animal.

As already discussed, the prior patent focuses on the intron sequences and teaches the use of DNA in homologous recombination and gene therapy. See, col. 8, ls. 12-22, and l.42 ff. over to col. 9, l.5, and claim 20 of the '962 patent. In addition, it claims an

anti-sense oligo for homologous recombination. See, claim 20. Thus, the '962 patent is clearly interested in DNAs for homologous recombination and gene therapy, particularly for administration into blood vessels. See above. A passing mention is made in the patent to treating cystic fibrosis with anti-sense oligos to the A_1 receptor. See, col.9, ls. 44-48, and col.11, ls. 24-26 of the prior patent. Applicant submits that what the prior patent has done is merely to list hypothetical potential applications of a known technology without any basis or guidance to lead an artisan to attain any positive results. Clearly, undue experimentation would be required to ascertain which fragments might be useful for what application, their respective method of administration, and their corresponding dosages. In re Dillon, (CAFC), 16 USPQ2d 1897, (1990).

Moreover, even though the '962 patent lists generic anti-sense oligos said to be 10-60 nucleotide long, it provides no guidance as to how to select the fragments, nor which specific sequences are intended. Clearly, a sparsity of disclosure and lack of reduction to practice would determine the absence of fragments in the claims. In summary, the '962 patent contains insufficient disclosure to enable, or even suggest, specific fragments other than the anti-sense polynucleotides extending the entire sequence of the introns. Finally, there is no reference in the '962 patent to an areosol composition as claimed here.

Finally, applicant has taken the art of designing therapeutic anti-sense oligos a step further than the prior art. He has gone where no one had gone before and attained 100% success, as evidenced by the enclosed Declarations. The prior art simply fails to both disclose and suggest the claimed invention. Because of this, applicant is entitled to a patent broadly claiming his product, its therapeutic application, and kits for therapeutic use.

The pending claims free from the above rejection.

THE THIRD ANTICIPATION REJECTION

Claims 1-7, 15-17, 23-28, 30, 34-37, 40, 53-54, 65-75, 80-81, 83, 88-90, 94 and 102-103 stand rejected under 35 USC 1.102(b), allegedly as being anticipated by US Patent No. 5,514,788 to Bennett. This rejection is also traversed.

Bennett is different from the claimed invention, and fails to render it obvious.

Nowhere does the Bennett patent describe or suggest the claimed composition, kit or treatment with an aerosol formulation comprising particles of an oligo anti-sense to a DNA encoding a protein associated with hyper-reactivity to or increased levels of adenosine, bronchoconstriction, allegies or inflammation or the corresponding mRNA, let alone one also aomprising a surfactant with the required activity.

Bennett has three claims directed to sequences that neither anticipate nor render the claimed composition obvious. The Bennett invention relates to the modulation of cell adhesion molecules. See, for example, last two lines of the Bennett abstract. Nowhere does the Bennett patent disclose or suggest employing an aerosol composition of anti-sense oligos to adenosine receptor targets, with or without a surfactant. Nor does Bennett disclose or suggest treating a subject by administering to his\her airways an aerosol formulation comprising oligonucleotides of any type.

The above rejection is believed to be moot in view of the above remarks in so far as it applies to the pending claims.

THE FOURTH ANTICIPATION REJECTION

Claims 1-107 stand rejected under 35 USC 1.102(e), allegedly as being anticipated by US Patent No. 5,994,315 (the '315 patent) to the present inventor. This rejection is traversed as well.

The present application claims priority of the filing date of the cited application. But in addition, the claimed invention is clearly distinguishable over the '315 patent, which thus fails to render the claimed invention obvious. The present application claims priority to the filing date of the '315 patent.

The above rejection is believed to be moot in view of the above remarks.

THE OBVIOUSNESS REJECTION

Claims 8-13 stand rejected under 35 USC 103(a), allegedly as being rendered obvious by Nyce et al. (which one?) in view of Jacobson. This rejection is traversed.

Although the references cited are Nyce et al. and Jacobson, the examiner's comments relate to Stiles and Brackett. Upon reading the text of the arguments, the examiner proposed to withdrew the rejection since she could not explain its presence in

the text of the Action.

However, as discussed above, the '962 patent is different from the claimed invention, and fails to render it obvious. The '962 patent relates solely to phosphodiester oligonucleotides whereas applicant's claims reflect a selection invention encompassing non-phosphodiester oligonucleotides which have been shown to be unexpectedly superior than their phosphodiester analogues. Nor does the '962 patent provide for any kind of substitution to the natural sequences of the oligo, and it relates solely to the human adenosine A_1 receptor, not to the adenosine A_1 receptor from any other species. Thus, anti-sense oligos generally described by the '962 patent are specific to the human adenosine A_1 receptor mRNA, not the A_3 receptor mRNA. See, Section 8, or col.1 of the '962 patent. Further, the anti-sense sequences must bind specifically to one of the above-indicated three DNA sequences, although the claims require the anti-sense oligos to specifically hybridize to introns 1 to 5 of the gene encoding the human adenosine A_1 receptor (SEQ. ID No.: 6) under highly stringent conditions. See, (b) of Claim 17 of the '962 patent. The described conditions are utilized solely in vitro, since they would never be encountered in vivo. More over, there is no mention in Stiles to adding a surfactant to aid the up-take of the oligo. Thus, the '962 patent also fails to teach how to administer the oligos to a living animal, and neither describes nor suggests the claimed composition or method.

As already discussed, the prior patent focuses on the intron sequences and teaches the use of DNA in homologous recombination and gene therapy. See, col. 8, ls. 12-22, and l.42 ff. over to col. 9, l.5, and claim 20 of the '962 patent. In addition, it claims an anti-sense oligo for homologous recombination. See, claim 20. Thus, the '962 patent is clearly interested in DNAs for homologous recombination and gene therapy, particularly for administration into blood vessels. See above. Although a passing mention is made in the patent to treating cystic fibrosis with anti-sense oligos to the A_1 receptor, this reference is not enabledby experimental showing; nor is there a showing relating to receptor mRNAs associated with hyper-responsiveness to or higher levels of adenosine, bronchoconstriction, allergies and/or inflammation. See, col.9, ls. 44-48, and col.11, ls. 24-26 of the prior patent. More particularly, the '962 patent fails to disclose any use of aerosol compositions of anti-sense oligos in the treatment of respiratory diseases, let

alone asthma, inflammation of the lungs or any of the remaining diseases listed here. What the prior patent has done is merely lising hypothetical potential applications of a known technology without any basis or guidance to lead an artisan to attain any positive results. Clearly, undue experimentation would be required to ascertain which fragments might be useful for what application, their respective method of administration, and their corresponding dosages. In re Dillon, (CAFC), 16 USPQ2d 1897, (1990). Thus, the '962 patent fails to lead an artisan to the applicant's anti-sense oligos or to their administration as an aerosol for the treatment of the described disorder. **The art prior to applicant's invention neither taught nor suggested the administration of <u>any</u> aerosol composition of anti-sense DNA for the treatment of <u>any disease</u>.** In fact, as stated above, an artisan would have been lead away from directly administering anti-sense oligos to the lungs given the high doses administered by others, both intravenously and systemically. This argument is supported by the fact that applicant's Nature (1997) publication represents the first application of antisense oligonucleotides directly to the lung reported in the literature, even though very extensive work, including clinical trials with antisense oligonucleotides, has been reported in the literature. Thus, the effectiveness of the lung as a target for antisense oligonucleotides was completely unexpected.

Jacobson is also different from the claimed invention, and fails to cure the defficiencies of Nyce et al. Stiles was discussed above as was its failure as a prior art reference to anticipate or render obvious the claimed invention. Brakett, as Ali et al. And others before them, discloses the application of several xanthines for tracheal relaxation. As the examiner points out some were more efficacious and some less. However, they were known, as was their preparation and use. But even if, arguendo, Nyce et al., Jacobson, the '962 patent, Ali. et al. And the Brackett reference were to be combined, they would not render the claimed invention obvious. Infact this combination would only lead an artisan to try, by experimenting with the adenosine A1 receptor target, different segments, different routes of administration and different formulations. But given the overall uncertainty of the biological field, it is highly unlikely that an artisan would arrive at the applicant's specific anti-sense oligos targeted to the adenosine A_1 receptor mRNA, and would administer them as an aerosol in the small dose utilized by applicant. Even if,

as the examiner may argue, it is obvious to try, it is by all means not obvious to attain applicant's 100% experimental success.

On the other hand, applicant's composition targeting the adenosine receptor mRNA and requiring a surfactant is distinct from each of the cited references and of their combination and, therefore, neither anticipated nor rendered obvious by them. In fact, applicant has taken the art of designing therapeutic anti-sense oligos a step further than the prior art. He has gone where no one had gone before and attained 100% success. The prior art simply failed to both disclose and suggest the claimed invention. Because of this, applicant is entitled to a patent broadly claiming his product, its therapeutic application, and kits for therapeutic use.

Jacobson is also different from the claimed invention, and fails to provide the link which is missing from the '962 patent, Nyce etv al. and Brackett. **Jacobson et al. relate to the adenosine A_3 receptor protein and cDNA, but fail to disclose any sequences for the adenosine A_3 receptor gene.** Jacobson et al. also provide the cDNA and protein sequences for the adenosine A_1, A_{2a}, A_{2b} receptors, but not their genomic sequences.

Jacobson discusses the role of A_1 and A_3 adenosine receptors in diseases and discusses methods to identify receptor agonists and antagonists, the latter being small molecules not antisense oligos. As discussed above, the one or more roles of these receptors in disease have been known for many years prior to Jacobson et al. Applicant, however, has been unable to find either comments or a teaching in Jacobson et al. for identifying specific agonists and antagonists, except perhaps a passing mention of a general desire in the following section:

The recombinant adenosine receptors may be utilized in an assay to identify and evaluate entities that bind to or enhance binding to adenosine receptors. See, Abstr. of Jacobson et al. Clearly, Jacobson et al. were looking for receptor agonists or antagonists which bind to or enhance binding to adenosine receptors, not DNA oligomers which bind to adenosine receptor mRNAs, as applicant did. Jacobson et al. go on to state that: Pure adenosine receptors make possible the identification and evaluation of compounds which have unique affinity for a single receptor subtype. Moreover, because of the variable effects of adenosine documented in other species, the utilization of human adenosine receptor subtypes is advantageous for the development of human therapeutic adenosine

receptor agonists, antagonists or enhancers. See, paragraph bridging pages 2-3 of Jacobson et al. These statements clearly express a generic desire for compounds that act at the receptors and enhance or antagonize their activities, whereas applicant down regulates the expression of the receptors' genes or mRNAs. But even when Jacobson et al. mention "antagonists", it is only as an invitation to search for such compounds, without providing an enabling method or guidance to do so. Most notably, there is no mention in all of Jacobson et al. of the actual words: anti-sense oligonucleotides.

The examiner has attempted to reproduce the applicant's invention by picking and choosing bits and pieces of different references, intended for significantly different purposes, and thrown them together with the hindsight provided by applicant's confidential disclosure. This is not permissible under the US Patent Law. But, in addition, the examiner has erred in the selection of the references. This rejection adds Jacobson et al. And Brackett to the previously applied references. They provide neither the genomic sequence nor any teaching to "discover" compounds acting at the receptors, let alone anti-sense oligos.

If the combination of the '962 patent with Jacobson et al., Nyce et al. And Brackett clearly adds nothing further. The examiner, thus, is thanked for withdrawing the above rejection in view of the above discussion.

Moreover, as already discussed above, the Nyce Declarations provide data on additional anti-sense oligo sequences, which have specificity for different segments of various receptor encoding mRNAs. The anti-sense oligos were designed and prepared as taught in the present application. The reported findings fully enable the scope of the invention encompassed by the present claims, and distinguish over the prior art. The examiner, therefore, is invited to consider the Nyce Declarations in the context of the above rejection.

THE DOUBLE PATENTING REJECTION

Claims 1-107 stand rejected under the Judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-105 of US Patent 5,994,315, and all claims of USSNos. 08/472,527 and 08/757,024 (now US Patents 6,025,339 and 6,040,296.

The claimed invention is clearly distinguishable from and, therefore patentable over, the prior patents by the present inventor. However, in view that priority of the filing date of the cited patent applications is claimed in this application, the applicant is herewith submitting an Assignment and Terminal Disclaimer, which renders the above rejection moot.

THE SEQUENCE LISTING SECTION

During the interview the examiner provided the applicant's attorney with a copy of the objections to the sequence listing.

The applicant is enclosing a corrected Sequence Listing section in paper and computer readable form along with the requisite Declaration. The listing includes additional sequences appended to the text of this application based on the text of the parent case: USSN 08/474,497, filed June 7, 1995, priority of the filing date of which is claimed here.

THE CLAIM FOR PRIORITY

The applicant is claiming priority by means of an accompanying document of the filing dates of the following U.S. Patent Applications.

1- U.S.S.N. 08/472,527, filed June 7, 1995, now U.S. Patent No. 6,040,296.
2- U.S.S.N. 08/757,024, filed November 26, 1996, by Jonathan W. Nyce, now U.S. Patent No. 6,025,339, which is a continuation-in-part of U.S.S.N. 08/472,527, filed June 7, 1995, now abandoned.
3- U.S.S.N. 08/474,497 filed June 7, 1995, by Jonathan W. Nyce and W. James Metzger, now US Patent No. 5, 994,315.
4- U.S.S.N. 09/016,464 filed January 30, 1998 by Jonathan W. Nyce and W. James Metzger, now pending, which is a divisional of U.S.S.N. 08/474,497.

In addition, the text of the present patent application is being amended accordingly to reflect this event.

GENERAL REMARKS

A check for $55.- is enclosed for payment (small entity) of the fee for filing a

Terminal Disclaimer, a second check for $55.- is enclosed for payment of the fee for a first-month extension of time, a third check for $40.- is enclosed for payment of recordation of Assignment, and a check for $__ for the extra claims. No other fee is believed to be owed. However, the Assistant Commissioner is hereby authorized to charge any fees owed, or refund any excess, to Deposit Account No. **01-2520**, including a fee for an extension of time which, if needed, is hereby requested.

In view of the foregoing amendments and remarks, and of the filing of a Sequence Listing and Declaration, this application is believed to be in condition for examination and allowance. Early notice to this respect is solicited.

Respectfully submitted.
ARTER & HADDEN

May 4, 2000
Date

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